بسم الله الرحمن الرحيم

Major Metabolic Pathways of Glucose

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Metabolic Pathway

Definition

Site:

Cellular (tissue) and Subcellular

Reactions

Rate-limiting enzyme(s)

Regulatory mechanism(s):

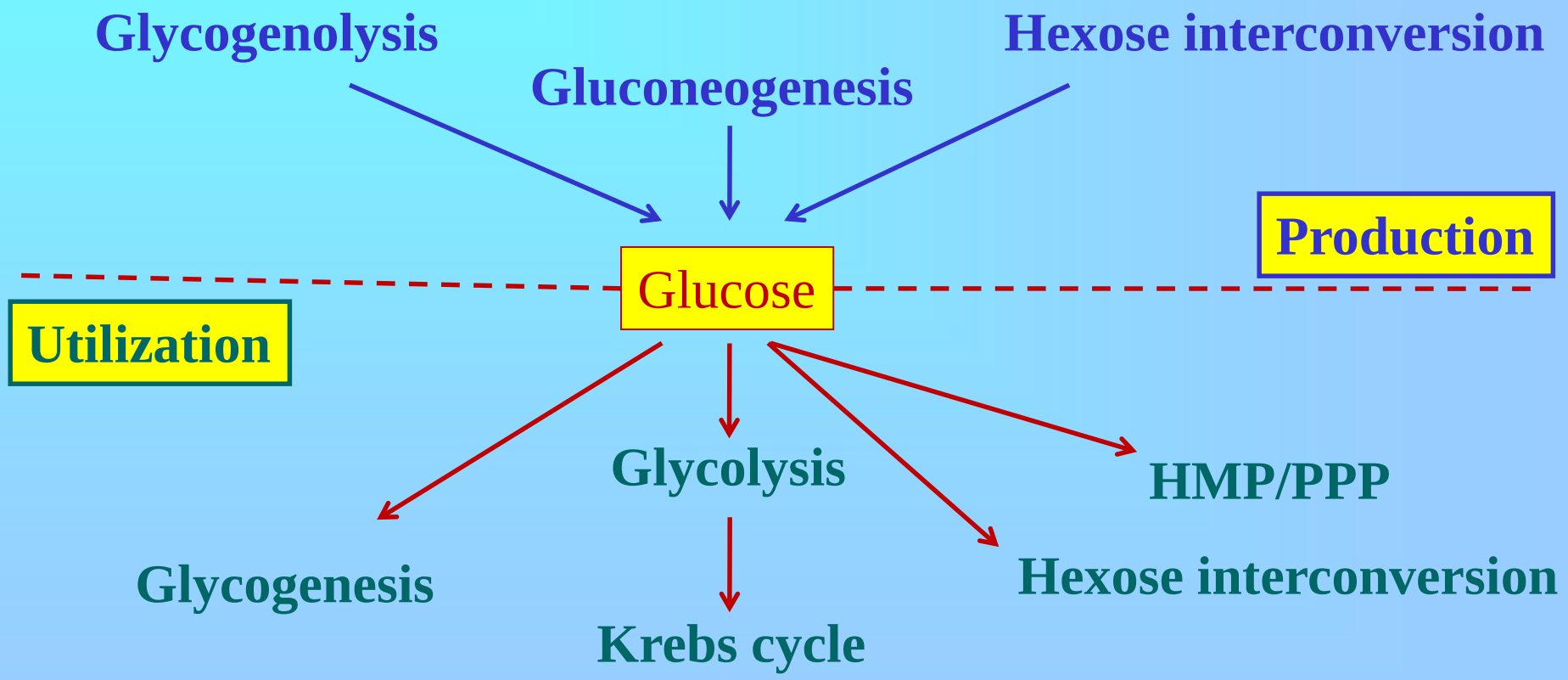
Rapid, short-term:

Allosteric **Covalent modification**

Slow, long-term:

Induction/repression

Metabolic Pathways of Glucose: Production and Utilization



Metabolic Pathways of Glucose: Catabolic and Anabolic

Catabolic cycles

- **Glycolysis (Mainly)**
- **Krebs (Mainly)**
- **Glycogenolysis**
- **HMP**

Anabolic cycles

- **Gluconeogenesis**
- **Glycogenesis**

Glycogenesis and Glycogenolysis

Glycogenesis:

Synthesis of glycogen from glucose
Mainly liver and muscle, Cytosol

Glycogenolysis

Degradation of glycogen into glucose
Mainly liver and muscle, Cytosol

Hexose Monophosphate Pathway (HMP) or Pentose Phosphate Pathway (PPP)

Important source for NADPH

Reductive syntheses

Source for metabolically active ribose

Production of nucleotides:

For nucleic acids

For co-enzymes

Glucose Transport

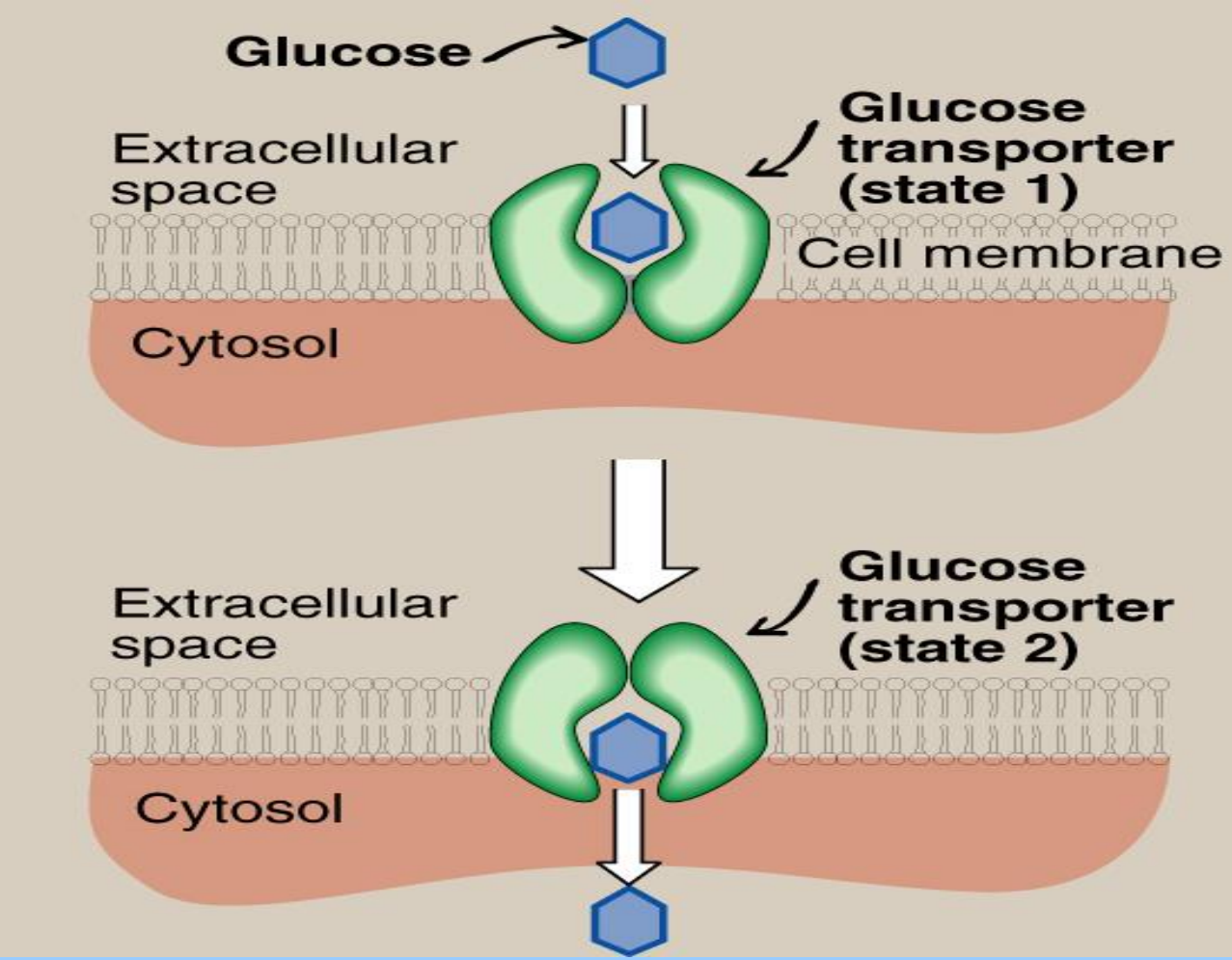
Na^+-Monosaccharide Cotransporter:

- Against concentration gradient
- Energy dependent
- Carrier-mediated
- Coupled to Na^+ transport
- Small intestine, renal tubules & choroid plexus

Na^+-Independent Facilitated Diffusion:

- With concentration gradient
- Energy Independent
- Glucose Transporters (GLUT 1-14)

Glucose Transport: Facilitated Diffusion



Glucose Transporters

- **Tissue-specific expression pattern**

GLUT-1	**RBCs and brain**
GLUT-2	**Liver, kidney & pancreas**
GLUT-3	**Neurons**
GLUT-4	**Adipose tissue & skeletal muscle**
GLUT-5	**Small intestine & testes**
GLUT-7	**Liver (ER-membrane)**

- **Functions:**

GLUT-1, 3 & 4	**Glucose uptake from blood**
GLUT-2	**Blood & cells (either direction)**
GLUT-5	**Fructose transport**

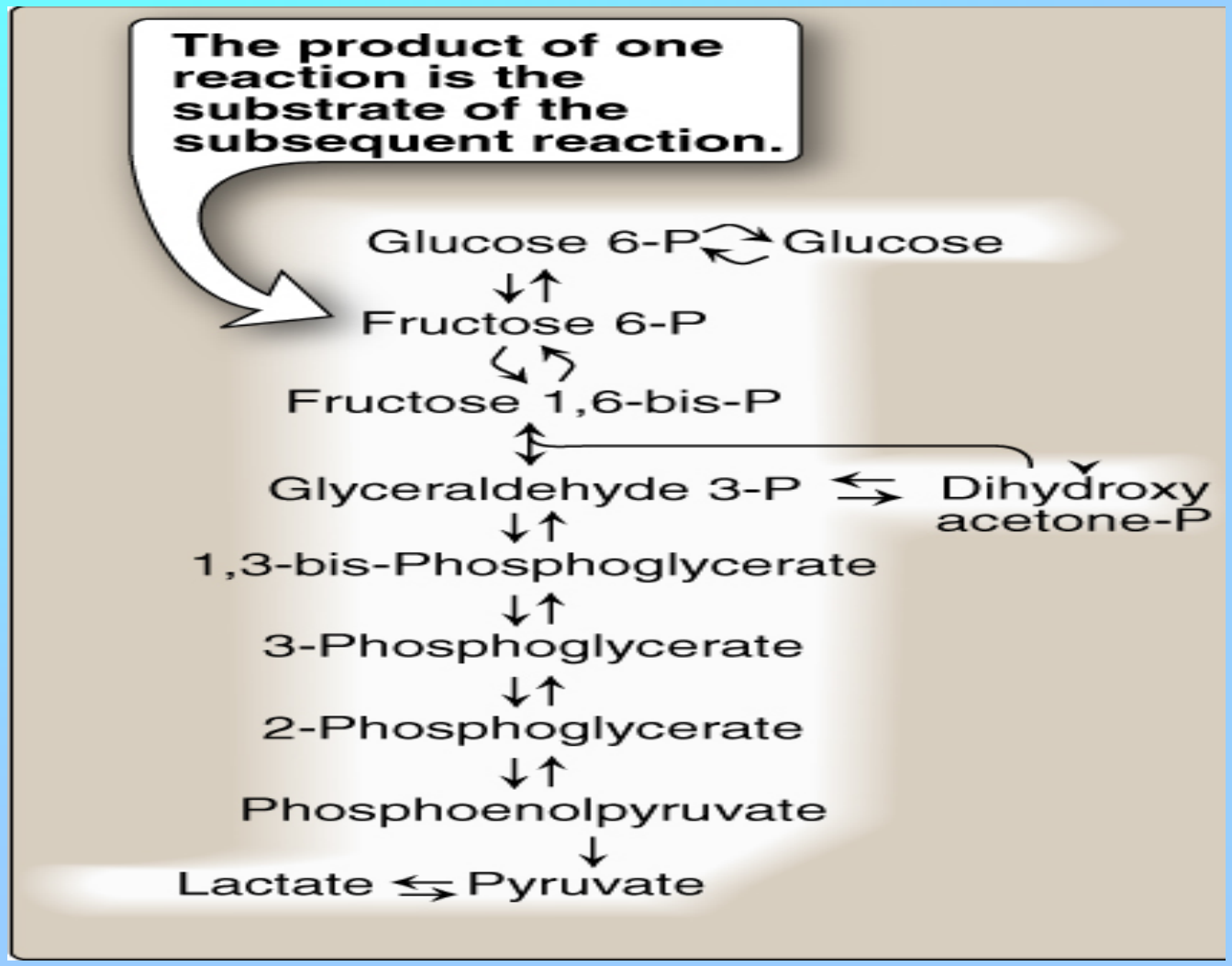
Glycolysis: Objectives

- Major oxidative pathway of glucose
- The main reactions of glycolytic pathway
- The rate-limiting enzymes/Regulation
- ATP production (aerobic/anaerobic)
- Pyruvate kinase deficiency hemolytic anemia

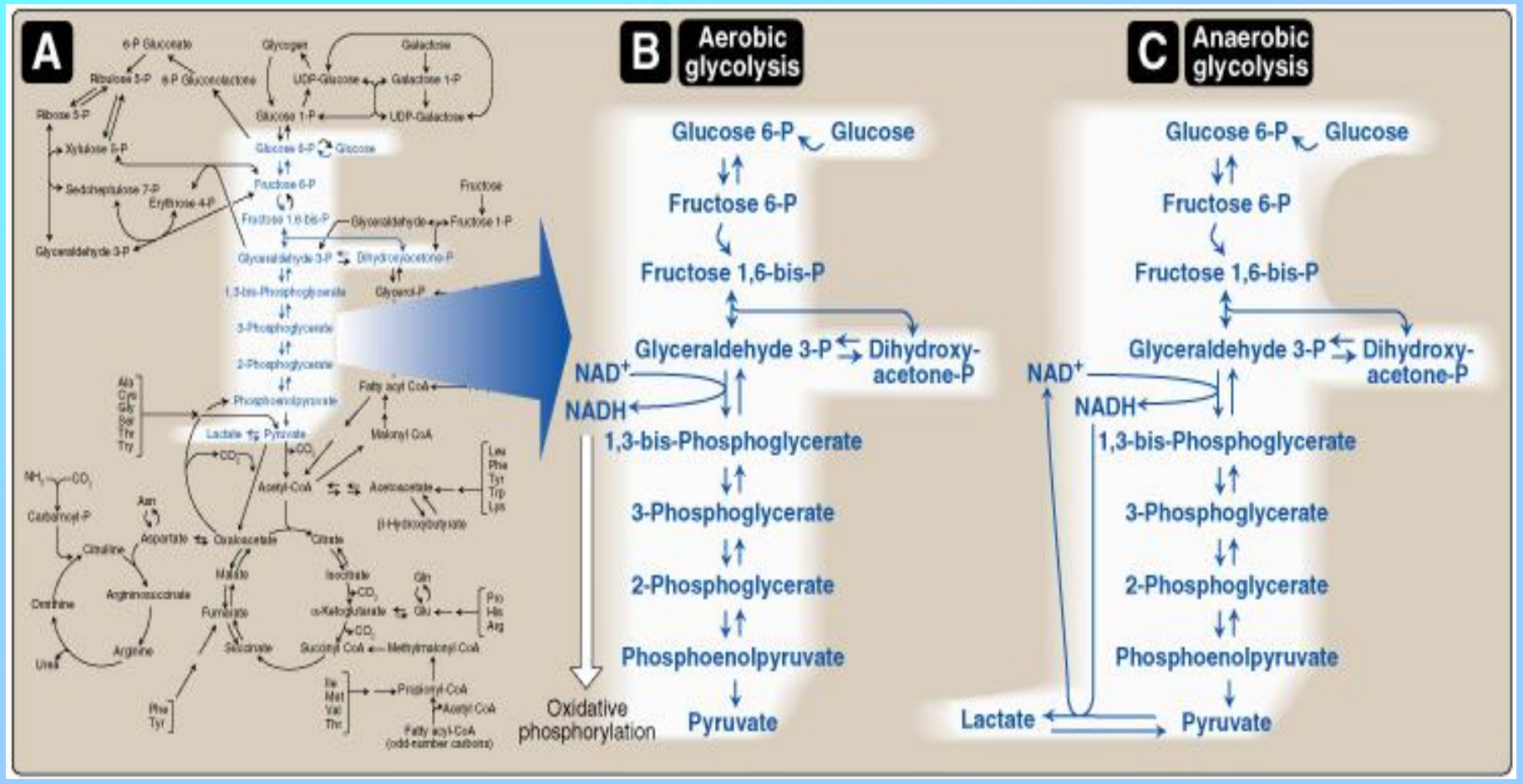
Glycolysis: An Overview

- Glycolysis, the major pathway for glucose oxidation, occurs in the cytosol of all cells.
- It is unique, in that it can function either aerobically or anaerobically, depending on the availability of oxygen and intact mitochondria.
- It allows tissues to survive in presence or absence of oxygen, e.g., skeletal muscle.
- RBCs, which lack mitochondria, are completely reliant on glucose as their metabolic fuel, and metabolizes it by anaerobic glycolysis.

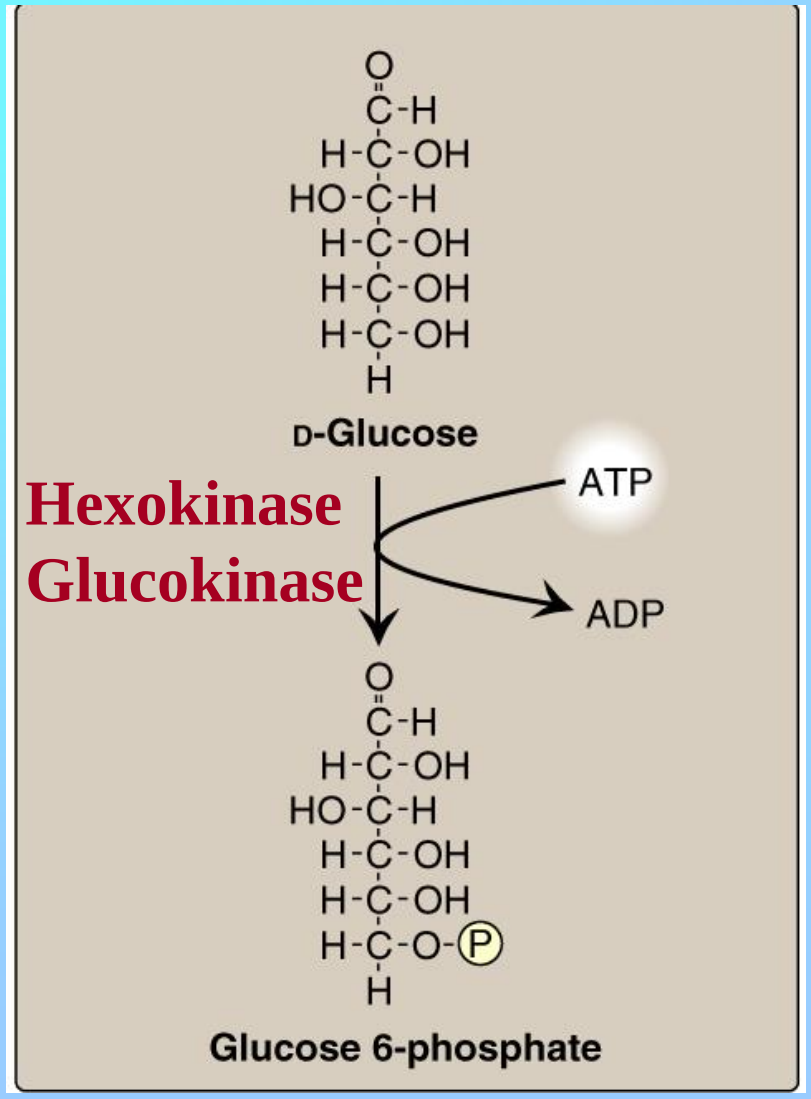
Glycolysis


The product of one reaction is the substrate of the subsequent reaction.
Glucose 6-P
Glucose
Fructose 6-P
Fructose 1,6-bis-P
Glyceraldehyde 3-P
Dihydroxy acetone-P
1,3-bis-Phosphoglycerate
3-Phosphoglycerate
2-Phosphoglycerate
Phosphoenolpyruvate
Lactate
Pyruvate

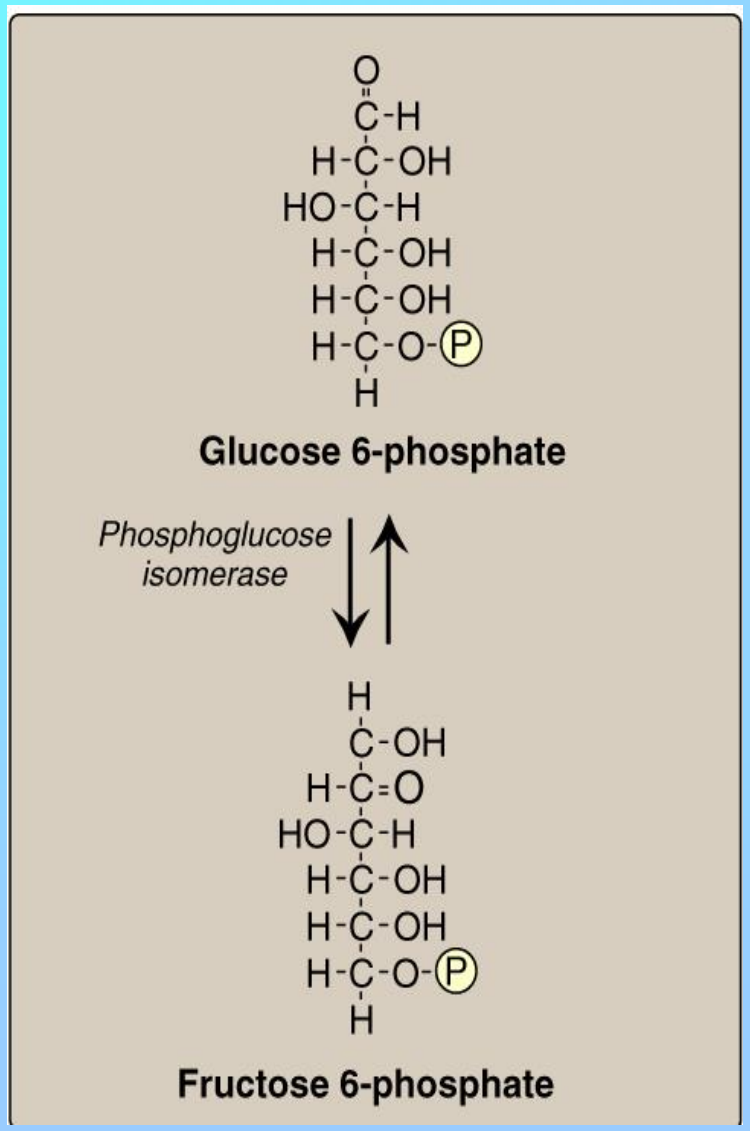
Aerobic Vs Anaerobic Glycolysis



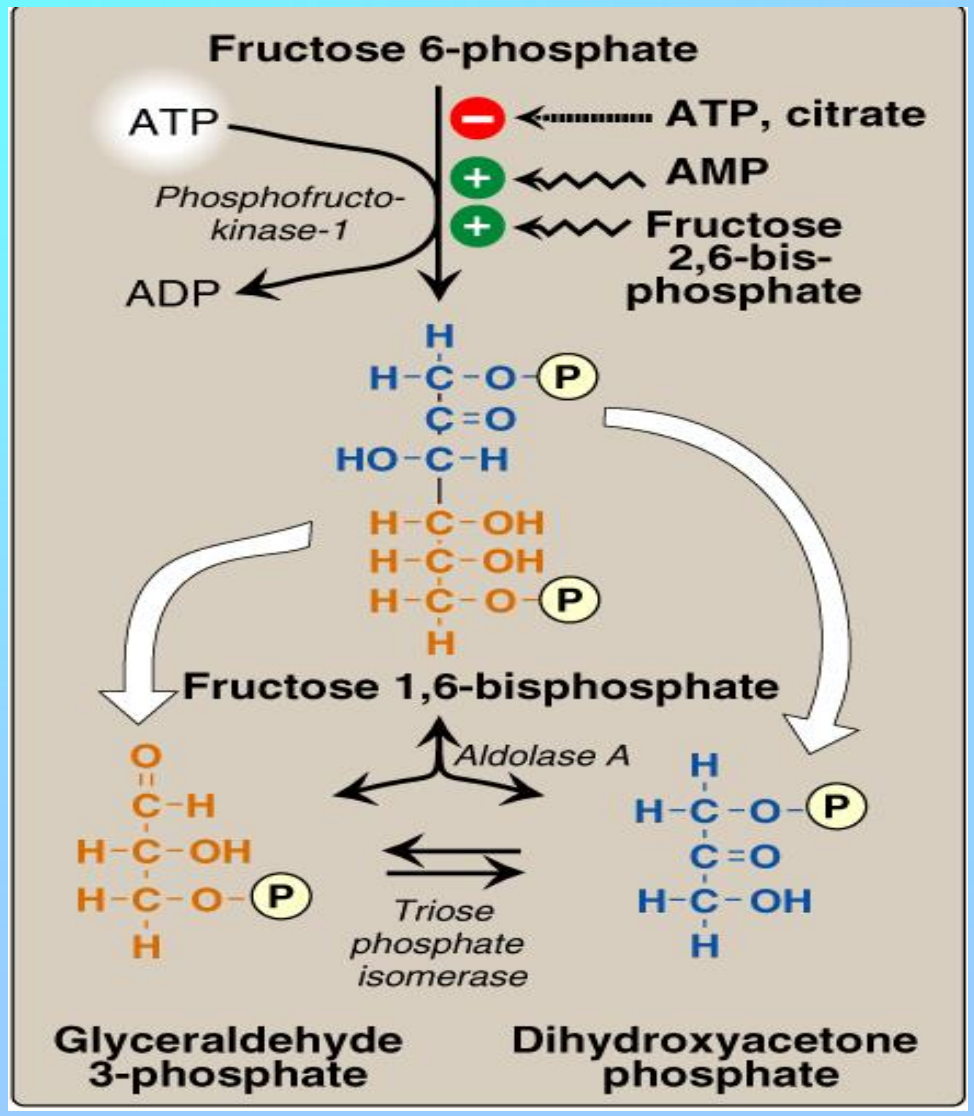
Aerobic Glycolysis-1



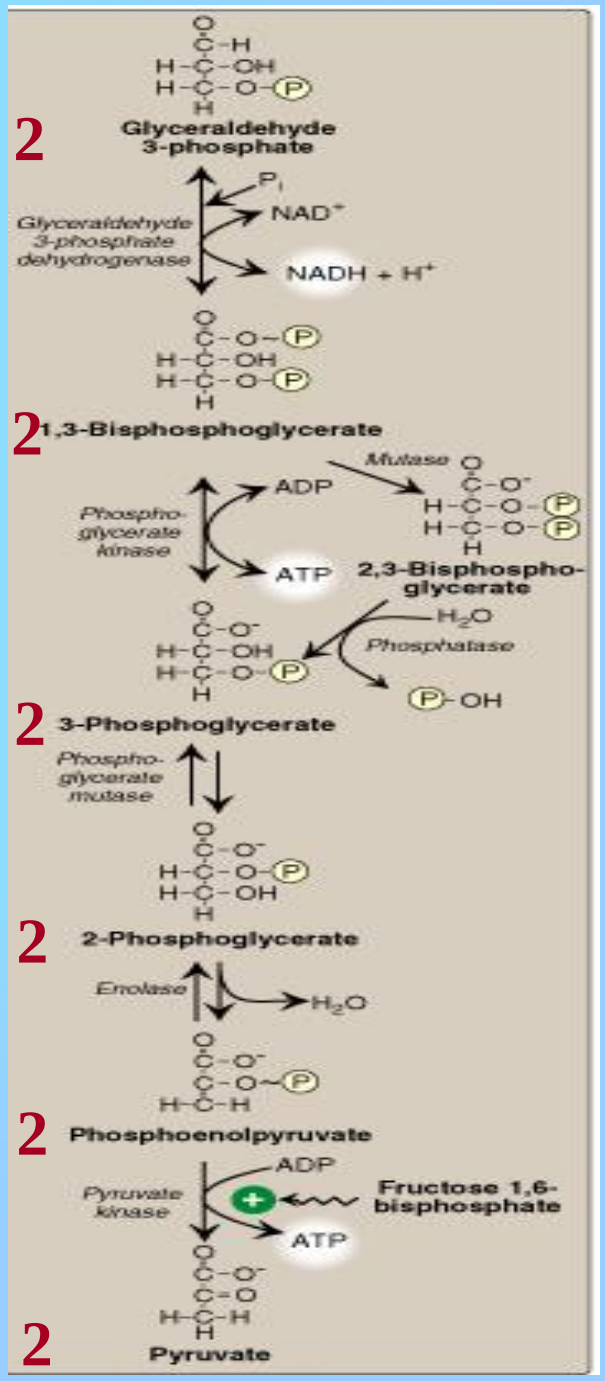
Aerobic Glycolysis-2



Aerobic Glycolysis: 3-5



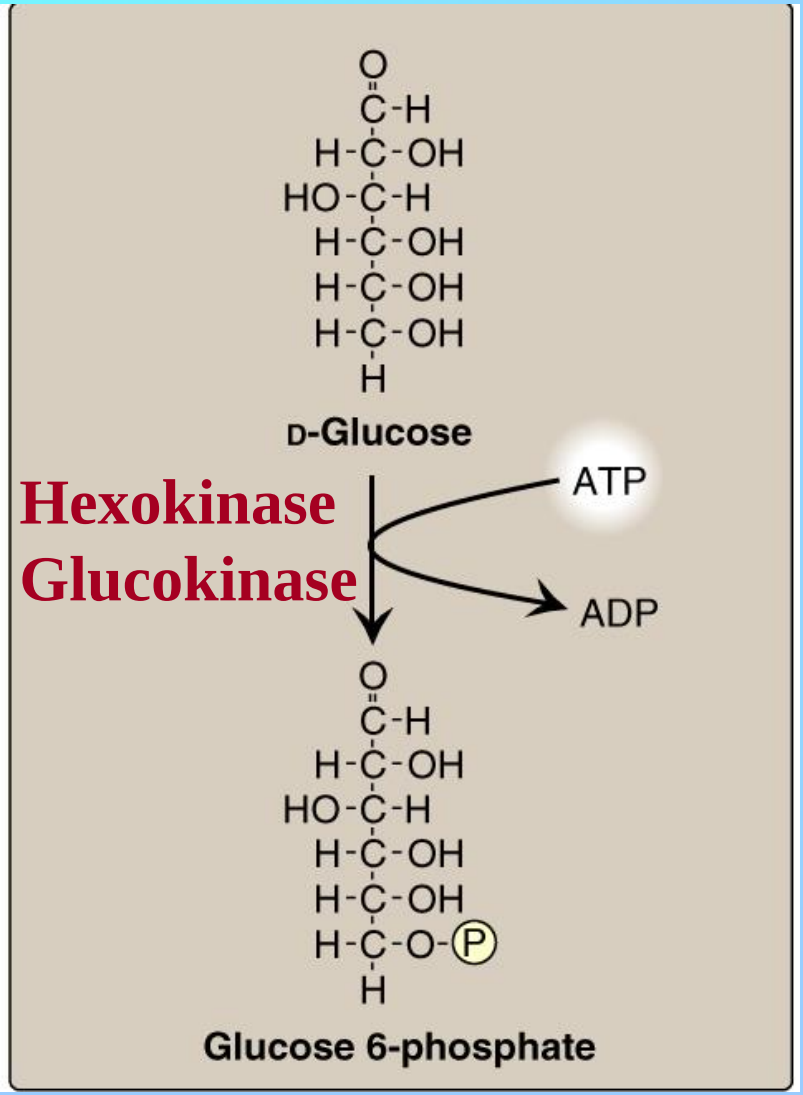
Aerobic Glycolysis: 6 -10



Aerobic Glycolysis-1

Hexokinase:
Most tissues

Glucokinase:
Hepatocytes



PFK-1 : Regulation

(1) Allosteric Regulation

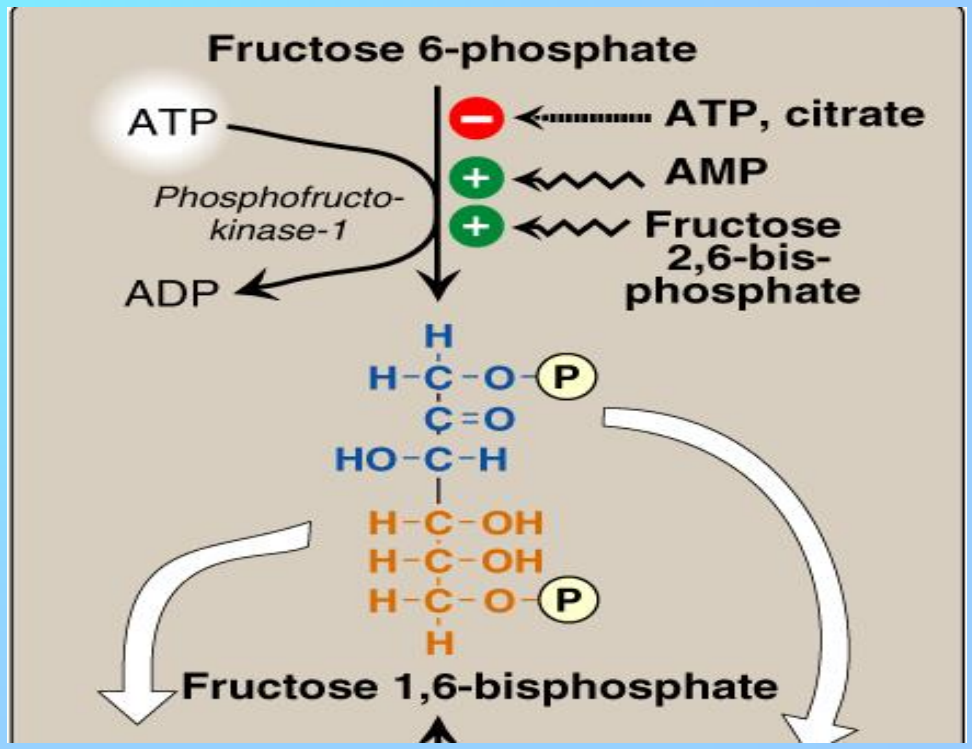
Inhibited: ATP & citrate

Stimulated: AMP & F2,6 bis Ⓟ

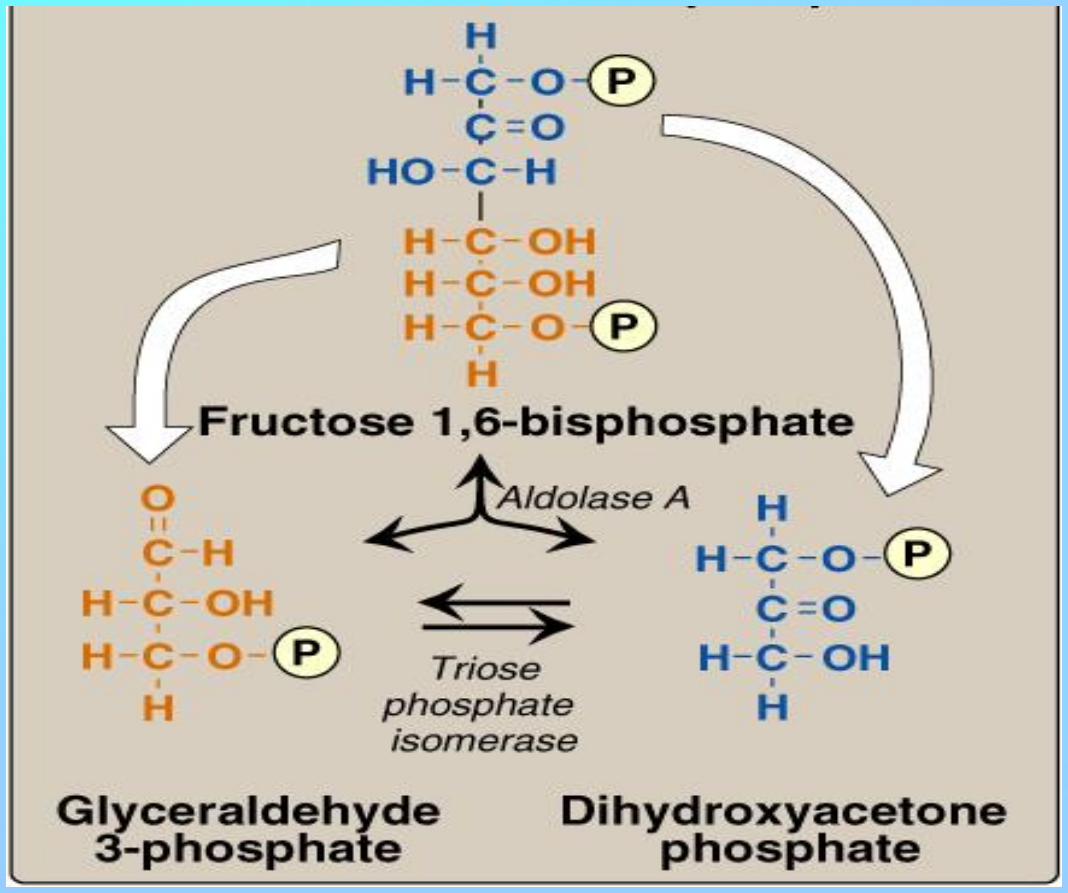
(2) Induction/Repression

Induced by insulin

Repressed by glucagon

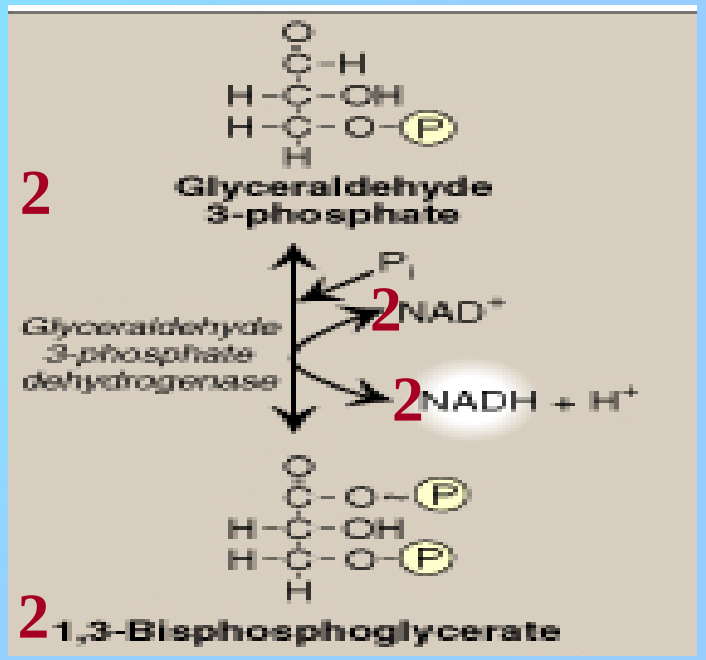


Aldolase and Triose Isomerase

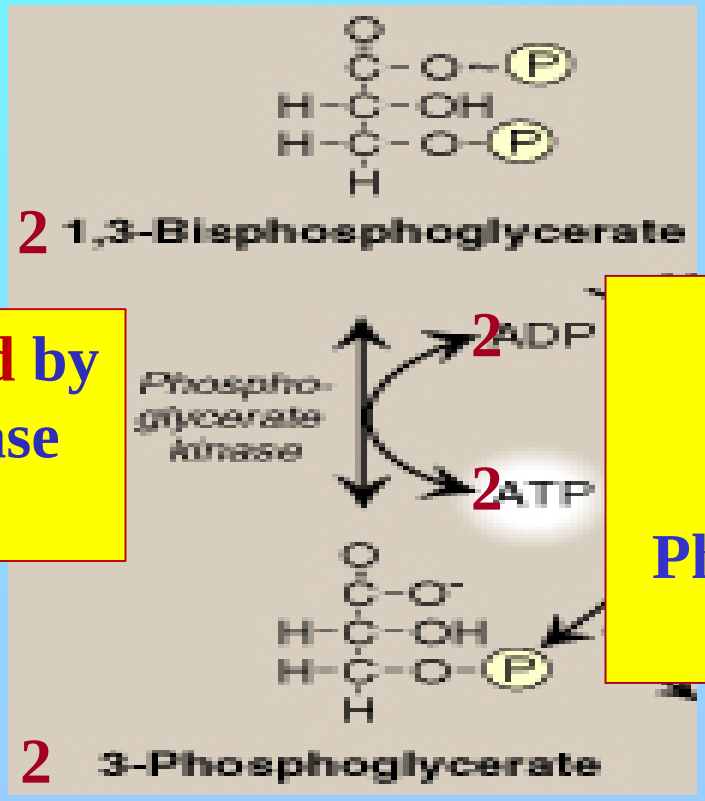


Glyceraldehyde 3-Phosphate Dehydrogenase

Two NADH are produced:
For each NADH, 3 ATP will be produced by ETC in the mitochondria
i.e., 6 ATP are produced by this reaction of aerobic glycolysis



Phosphoglycerate Kinase

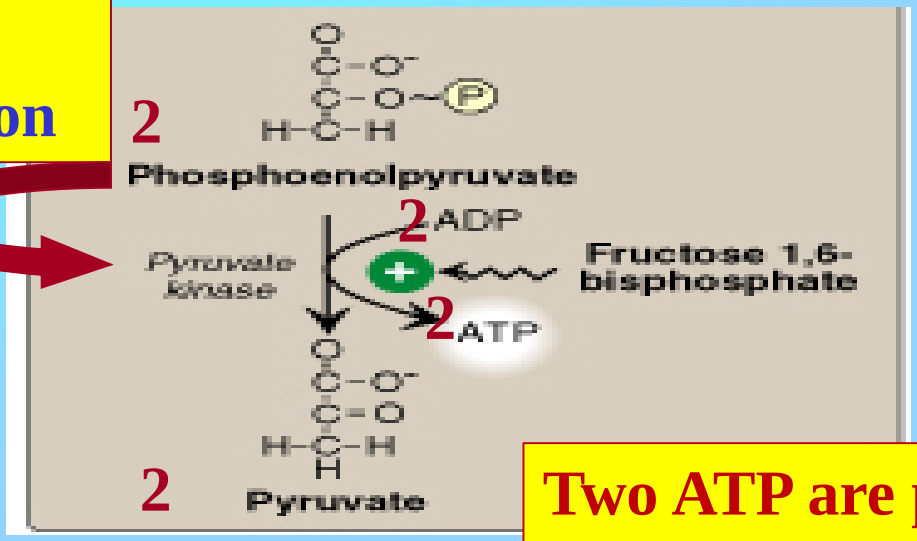


Two ATP are produced by phosphoglycerate kinase reaction of glycolysis

Substrate-Level Phosphorylation

Pyruvate Kinase

Substrate-Level Phosphorylation



Two ATP are produced by pyruvate kinase reaction of glycolysis

Substrate-level phosphorylation Vs. Oxidative phosphorylation

- **Phosphorylation** is the metabolic reaction of introducing a phosphate group into an organic molecule.
- **Oxidative phosphorylation:** The formation of high-energy phosphate bonds by phosphorylation of ADP to ATP coupled to the transfer of electrons from reduced coenzymes to molecular oxygen via the electron transport chain (ETC); it occurs in the mitochondria.
- **Substrate-level phosphorylation:** The formation of high-energy phosphate bonds by phosphorylation of ADP to ATP (or GDP to GTP) coupled to cleavage of a high-energy metabolic intermediate (substrate). It may occur in cytosol or mitochondria

Regulation: Pyruvate Kinase

Allosteric Regulation:

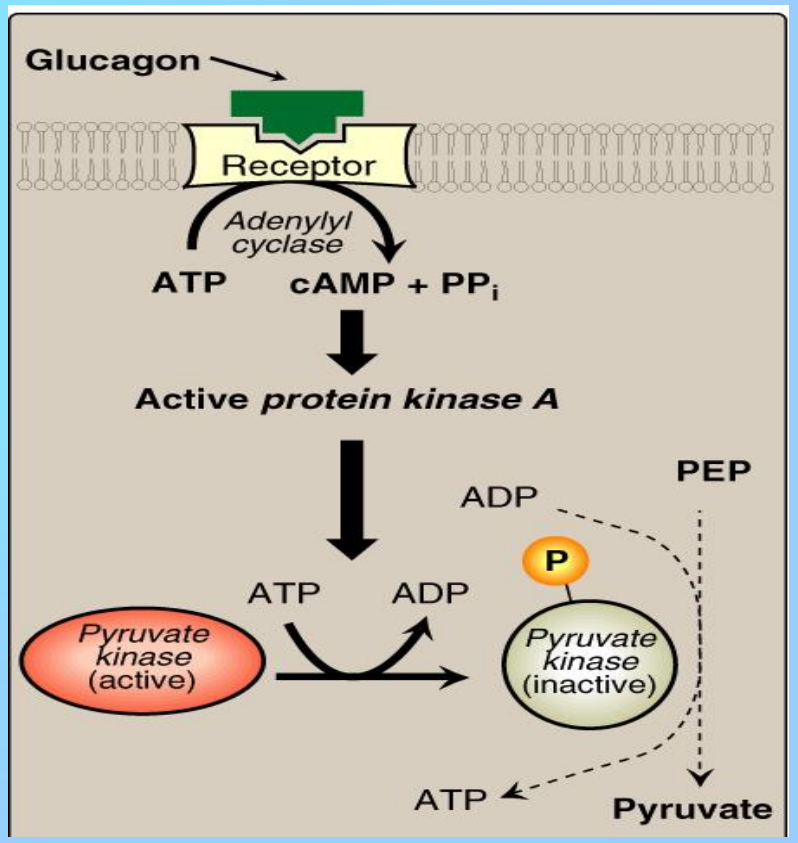
Feed-forward by F1,6 bis Ⓟ

Covalent Modification:

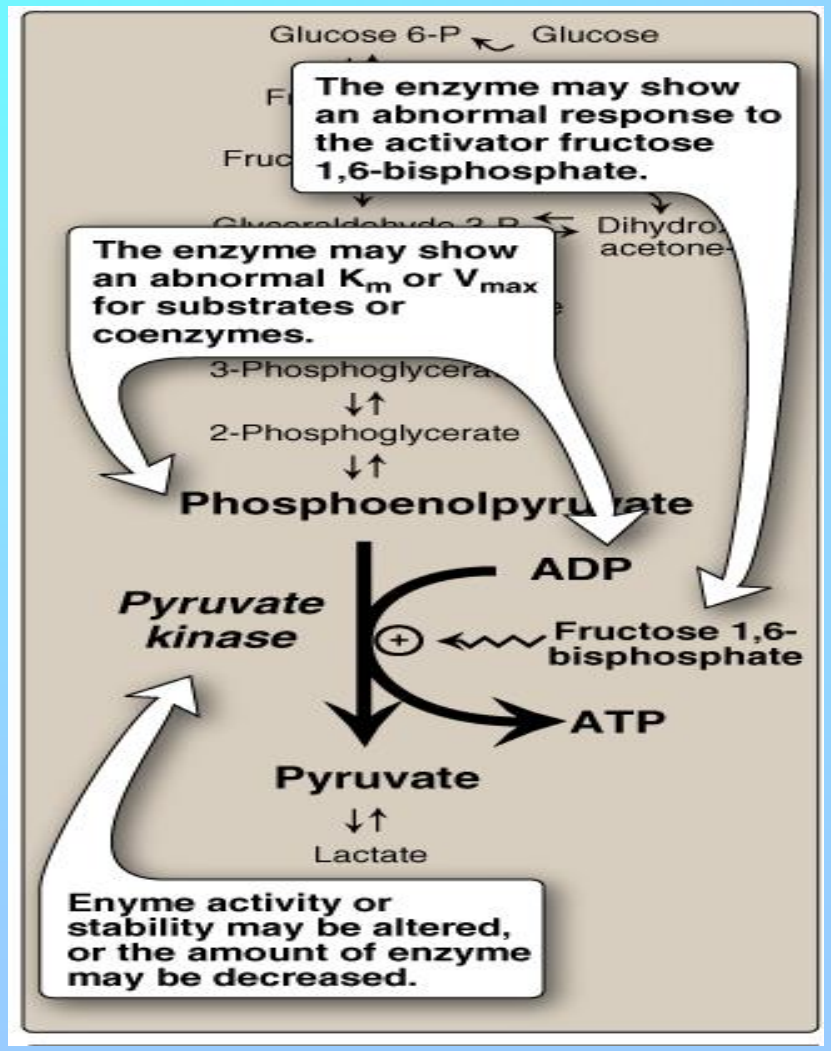
Active pyruvate kinase:
Dephospho-form

Induction/Repression:

Induced by insulin
Repressed by glucagon



Pyruvate Kinase Deficiency Hemolytic Anemia



Summary: Regulation of Glycolysis

Regulatory Enzymes (Irreversible reactions):

- Glucokinase/hexokinase
- PFK-1
- Pyruvate kinase

Regulatory Mechanisms:

- Rapid, short-term:
  - Allosteric
  - Covalent modifications
- Slow, long-term:
  - Induction/repression

Apply the above mechanisms for each enzyme where applicable

Aerobic Glycolysis: ATP Production

ATP Consumed:

		2	ATP

ATP Produced:

Substrate-level	2 X 2 =	4	ATP
Oxidative-level	2 X 3 =	6	ATP
Total		10	ATP

Net:	10 – 2 =	8	ATP

Take Home Message

- **Glycolysis is the major oxidative pathway for glucose**
- **Glycolysis is employed by all tissues**
- **Glycolysis is a tightly-regulated pathway**
- **PFK-1 is the rate-limiting regulatory enzyme**

Take Home Message

- **Glycolysis is mainly a catabolic pathway for ATP production, But …..**
- **It has some anabolic features (amphibolic)**
- **Pyruvate kinase deficiency in RBCs results in hemolytic anemia**

THANK YOU